PROJECT NUMBER: 2520
PROJECT TITLE: Flavor Research
PROJECT LEADER: E. W. Southwick
PERIOD COVERED: April, 1988

I. GLUCOSE-DERIVED FLAVORANTS

A. **Objective**: To develop glucose-derived flavorants.

B. **Results**: (1) Menthol-glucose carbonate. Reaction of glucose and 1-menthyloxycarbonylimidazolide in either pyridine or dimethylformamide in the presence of about 20 mol% of 1,8-diazabicyclo[5,4,0]undec-7-ene produced a reaction mixture which consisted of mainly 6-O-, 2-O- and β-1-O-menthyloxycarbonyl-D-glucoses, with the 6-O-isomer being the more abundant one. The 4th isomer was identified by C-13 NMR as the 3-O-menthyloxycarbonyl-D-glucose. The concentration of this isomer is relatively small compared with the others. However, its presence interfered with the chromatography such that a realistic estimation of the isomer distribution is not possible.

(2) Glycoside Synthesis. Reaction of phenethyl alcohol with N-iodosuccinamide and 3,4,6-tri-O-acetyl-D-glucal in acetonitrile gave a 55% yield of phenethyl 3,4,6-tri-O-acetyl-2-deoxy-2-iodo-α-D-mannopyranoside. This reaction is designed as one of the model reactions leading to the total synthesis of the natural "sucrose ester".

Reaction of 2-ethoxy-5-(1-propenyl)phenol with 1,2,3,4,6-penta-O-acetyl-D-β-D-glucopyranose in benzene with a catalytic amount of boron trifluoride etherate gave a modest yield of the corresponding β-glucopyranoside. After removal of the blocking groups, the 2-ethoxy-5-(1-propenyl)phenyl β-D-glucopyranoside so obtained will be submitted as a candidate for mainstream/side-stream analysis.

(3) Spray-dried flavorants. A Yamato GB-22 Spray Dryer was received and put into operation. Trial runs using sodium chloride solutions were successful. Trial runs using glucose or sucrose solutions were far from satisfactory. The final products, being somewhat hygroscopic, tend to absorb some moisture and adhere strongly to the side of the vessel. Solutions of β-cyclodextrin were spray-dried successfully. The product also tends to adhere to the side of the vessel due to electrostatic charge. We are exploring various ways to minimize this phenomenon. In all the cases studied, the recovery is in the 60-70% range.

(4) Cyclodextrin complexes. Due to the recent cost reduction of β-cyclodextrin and a perceived need for a tetramethylpyrazine release agent, a complex of tetramethylpyrazine and β-cyclodextrin has been synthesized. A particular advantage to the use of the flavorant tetramethylpyrazine results from it having a high odor threshold and a low flavor threshold (Extra project, 0.5 ppm). The complex was synthesized by dissolving β-cyclodextrin in water

followed by addition of tetramethylpyrazine. The mixture was stirred for 24 hours at room temperature. The precipitate was filtered, washed with 95% ethanol and ether. The solid material was dried under vacuum (0.01 mm Hg) for 4 hours. A 37% yield (8 grams) of the complex was obtained. Tube thermolysis indicated that tetramethylpyrazine was released upon decomposition of β-cyclodextrin (250-300°C). The amount of complexed tetramethylpyrazine was 5% on a weight basis as determined by thermolysis and GC analysis utilizing an external standard of tetramethylpyrazine.

II. PROJECT EXTRA

A. **Objective**: To develop proprietary flavor additives for enhanced flavor perception in low delivery cigarettes.

B. **Results**: (1) 6-Methylhexahydro-2(3H)-furanone (CR-2643). An investigation into the large scale synthesis of the precursor to CR-2643 was conducted. The precursor to CR-2643 is 6-(ethoxycarbonylmethyl)-3-methyl-2-cyclohexen-1-one (1). The reaction of 3-methyl-2-cyclohexen-1-one (0.1 mole scale) with lithium diisopropylamide was conducted in tetrahydrofuran at -78°C utilizing ethyl bromoacetate. This reaction yielded approximately 14 grams (80%) of 1. If the reaction was repeated utilizing ethyl chloroacetate instead of ethyl bromoacetate no alkylated product 1 was obtained. The material isolated contained mainly starting material. The effect of temperature on this reaction was investigated. If the reaction was conducted at 0°C utilizing ethyl bromoacetate only a 51% yield of 1 was obtained with a considerable amount of polymeric material being formed. Therefore, a good yield of 1 can be obtained on a large scale if ethyl bromoacetate is used and the reaction is conducted at -78°C.

Reduction of 6-(ethoxycarbonylmethyl)-3-methyl-2-cyclohexen-1-one (PtO_2, acetic acid) and cyclization of the resulting hydroxy ester (acetic acid, heat) resulted in the isolation of 6-methylhexahydro-2(3H)-benzofuranone. This reaction procedure is simple and most importantly generates the title compound with a higher ratio of the trans isomer (cis/trans ratio 45/55). A 2.5 g sample of 6-methylhexahydro-2(3H)-benzofuranone (cis/trans 45/55) is now available.

(2) Acylpyrazines and derivatives. Acylation of 2,5-dimethyl-pyrazine with acetaldehyde gave the desired 2-acetyl-3,6-dimethyl-pyrazine in good yield following purification by reverse phase chromatography. Reduction of acylpyrazines with hydrazine gave the corresponding alkylpyrazines; 3,5,6-trimethyl-2-(3-methyl-1-butyl) pyrazine and 3,5,6-Trimethyl-2-n-propylpyrazine.

(3) Sidestream aroma. Several candidate flavorants have been evaluated in an effort to alter the perception of sidestream smoke. Evaluations are conducted using E-2 conference room. Seven cigarettes are injected with the odorant and stataically

burned in ashtrays. Panelists enter the closed room and rate overall intensity and amount of irritation on a 7-point scale. They also describe the odor. Cigarettes are extinguished and, 10 minutes later, panelists repeat the evaluation.

As expected the addition of flavorants at a high level (1500ppm) produces a distinct odor note to the smoke. However there is no significant reduction in intensity or irritation. Dose-response curves are being developed for a sub-set of these additives.

An alternative approach to the "distinctive" aroma is to develop a counteractant. In brief, by using a flavorant which blends with the smoke aroma, it may be possible to reduce intensity and irritation without delivering a "distinctive" aroma. At 160ppm, p-cresylisovalerate shows a small reduction in both intensity and irritation without a noticeable change in smoke aroma. Dose-response curves are being developed for this compound.